

REMARKS

I. Status of the Claims

Claims 1-38 were originally filed in the parent application. Subsequently, claims 1-11, 15, and 19-38 were canceled. Claims 12-14 and 16-18 remain pending under examination.

II. Information Disclosure Statement

The Examiner objected to the information disclosure statement submitted on March 31, 2004, indicating that references AE-AG and AL had not been considered for alleged failure to meet the requirement under 37 C.F.R. §1.98(b)(5). A new IDS is hereby submitted to place these references on file.

III. Claim Rejections

A. 35 U.S.C. §101

Claims 12-14 and 16-18 stand rejected under 35 U.S.C. §101 for alleged lack of patentable utility. The Examiner stated that the claimed invention has no apparent or asserted specific and substantial credible utility. Applicant respectfully traverses the rejection, for reasons already provided in Applicant's earlier responses and in view of the Rule 132 declaration by Dr. Krafte submitted herewith.

In the Final Office Action mailed August 23, 2006, the Examiner made several specific arguments to maintain the rejection under 35 U.S.C. §101. First, the Examiner argued that the utility requirement is not met because the present application "fails to identify a specific biological significance of the instant polypeptide ... and/or its association with any particular disease or pathological condition" and "fails to provide any evidence or sound scientific reasoning to support a conclusion that [the modulators] can be useful as therapeutic agents for treating diseases related to altered functions in tissues expressing Kv10 channels." See page 3 of the Action. Second, the Examiner further argued that utility is lacking because even if a compound is identified as a modulator of a Kv10 channel, an artisan would not know how to use the compound to treat a disease. See page 4 of the Action. Third, while conceding the identity of Kv10.1 (SEQ ID NO:3) as a potassium channel subunit and the physiological importance of

potassium channels, the Examiner continued to argue that the disclosure of a novel potassium channel is "meaningless without clear understanding of how to use this polypeptide." See pages 5-6 of the Action. Applicant respectfully disagrees with the Examiner on these points.

First of all, the Examiner's reasoning for the utility rejection erroneously places the initial burden to establish utility on Applicant. As already discussed in Applicant's last response (filed June 2, 2006), the presumption of utility meeting the requirement under 35 U.S.C. §101 arises once an applicant asserts a certain utility for his invention. To overcome this presumption, the Examiner must carry the initial burden to establish a *prima facie* showing of lack of utility by providing evidentiary basis supported by objective evidence or reasoning. MPEP §2107.02 III A and IV. It is therefore inappropriate for the Examiner to make the utility rejection by merely asserting that Applicant has not identified a specific disease associated with Kv10.1 or that Applicant has not provided proof of utility. Applicant is not required to carry the initial burden to establish utility; it is the Examiner who must carry the initial burden to establish lack of utility by evidence and reasoning.

Although not required to carry the initial burden of establishing utility of his invention, Applicant nevertheless submits a declaration pursuant to 37 C.F.R. §1.132 for this purpose. In his declaration, Dr. Douglas Krafte provides detailed explanation as to why the identification of Kv10.1 has a specific and substantial utility and why a person of skill in the art would find this utility credible, particularly in the context of drug discovery.

In his declaration, Dr. Krafte explains that several subfamilies of the Kv potassium channel family have previously been identified. These potassium channels are indicated in signal transduction during various biological processes such as neuronal integration, cardiac pacemaking, muscle contraction, hormone secretion, cell volume regulation, lymphocyte differentiation, and cell proliferation. Given this knowledge and the specific expression of Kv10.1 in the CNS, male reproductive organs, and retina, one of ordinary skill in the art would recognize the Kv10 channel as a therapeutic target for treating CNS or vision disorders or for regulating male infertility. In support of this statement, there is a recent publication describing mutations in the Kv10.1 gene (KCNV2) that are responsible for a specific vision disorder, which

is characterized by reduced visual acuity, photoaversion, night blindness, and abnormal color vision (Wu *et al.*, 2006 *Am. J. Hum. Genet.* **79**: 574-579, attached to the declaration as **Exhibit B**). The identification of human Kv10.1 coding sequence makes it possible to screen for activators and inhibitors of Kv10 potassium channels. Because such activators or inhibitors can be used for treating abnormalities in the relevant tissues (such as epilepsy, impaired vision, and male infertility), the present invention has a specific and real-world use. A further example of targeting potassium channel for therapeutic purpose is KCNQ2. Loss of function mutations of KCNQ2 have been shown to cause a form of epilepsy (Singh *et al.*, 1998 *Nat. Genetics* **18**: 25-29, attached to the declaration as **Exhibit C**) and the KCNQ2 channels have been targets for drug discovery programs for a number of years (see, *e.g.*, Wickenden *et al.*, 2004 *Expert Opin. Ther. Patents* **14**(4): 1-13, attached to the declaration as **Exhibit D**). See paragraph 6 of the declaration.

Dr. Krafte further states that it is well known in the art that once an ion channel has been identified, modulators of this ion channel can be routinely identified based on the coding sequence of the ion channel, functional expression, and a method for activation of the channel. The present application provides nucleic acid sequences encoding human Kv10.1 polypeptides as well as methods for activating a Kv10 potassium channel, one of ordinary skill in the art can thus conduct routine testing to identify activators or inhibitors of a Kv10 potassium channel useful for modulating signal transduction in the cells where this potassium channel is present (*e.g.*, the brain, spinal cord, prostate, testis, and retina), and therefore useful for treating neurological disorders and vision problems, or for modulating male fertility. See paragraph 7 of the declaration.

Dr. Krafte also explains that there are known instances where modulation of an ion channel is useful for treating a specific disease even though the channel itself may not cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure by blocking a calcium channel is useful and effective, even if the original cause of the

hypertension is unrelated to the calcium channel itself. Similarly, it is perfectly reasonable to expect that the targeting of a Kv10 channel, a voltage-gated potassium channel expressed at a high level in the CNS, ocular tissue, and male reproductive system, is an appropriate strategy for treating disorders in the CNS or vision, or conditions related to male fertility, whether or not such abnormality is directly caused by altered Kv10 activity. Thus, the disclosure of the present application is sufficient to establish the utility of Kv10.1. See paragraph 8 of the declaration.

Furthermore, Dr. Krafte points out that, in the Office Actions of March 2 and August 23, the Examiner apparently takes the position that the sequence information of Kv10.1 alone is insufficient to establish utility. Dr. Krafte notes, however, that this patent application provides not only sequence information, but also functional expression and tissue distribution for the Kv10.1 ion channel. He goes on to state that, in his experience, this disclosure provides the vital information necessary for a modern drug discovery effort where one expresses an ion channel of interest and subsequently identifies small molecule modulators of the ion channel in functional assays; the modulators can then be used for treating diseases and conditions relevant to the ion channel. According to Dr. Krafte, many of the drug discovery programs he has been associated with over the years have relied on a similar level of information and data. See paragraph 9 of the declaration.

Dr. Krafte concludes that, in his scientific opinion, one of skill in the art would, at the time this application was filed, recognize the specific and real-world utility of the Kv10.1 encoding nucleic acids of the present invention. Without any objective evidence or reasons contrary to this declaration, it is established that the present invention meets the utility requirement under 35 U.S.C. §101.

In making the second argument the Examiner has apparently confused the claimed subject matter of this application with something Applicant does not claim. The pending claims are directed to a nucleic acid encoding for a Kv subunit with a high level of sequence identity to human Kv10.1; they are not directed to a modulator of a Kv channel. As such, it is inappropriate for the Examiner to require a disclosure on what specific diseases are treatable by a Kv channel modulator in order to meet the utility requirement.

Contrary to the Examiner's contention, the manner Applicant describes the present invention is fully in compliance with the requirement under 35 U.S.C. §101. The Kv10 channel subunit encoded by the claimed nucleic acid is fully characterized both structurally and functionally: *e.g.*, having at least 90% identity to the amino acid sequence of SEQ ID NO:3 and capable of forming a voltage-gated Kv potassium channel with at least one additional Kv alpha subunit.

According to the Revised Interim Utility Guidelines Training Materials (the "Guidelines") promulgated by the PTO (<http://www.uspto.gov/web/menu/utility.pdf>), a characterized protein has sufficient utility for patentability. This standard is made evident from Example 8 on page 45 of the Guidelines, wherein a compound A is disclosed to inhibit enzyme XYZ, a well known enzyme, *in vitro*. The hypothetical specification states that the compound A can be used to treat diseases caused or exacerbated by enzyme XYZ. No such diseases are named. Claim 1 is directed to compound A. Claim 2 is directed to a method of treating a disease caused or exacerbated by enzyme XYZ consisting of administering an effective amount of compound A to a patient. In the subsequent analysis, claim 2 is deemed to be insufficiently supported by a real world context of use. This is because neither the specification nor the art of record discloses any disease or conditions caused or exacerbated by enzyme XYZ and therefore, the asserted utility is seen as a method of treating an unspecified and undisclosed disease or condition, which does not define a "real world" context of use. Claim 1, however, is regarded as having utility because claim 1 is directed to a compound that inhibits an enzyme and enzymes have well established utility in the art, *i.e.*, catalyzing certain reactions.

This hypothetical example can be compared to the present application. The present application claims a nucleic acid encoding a Kv10 channel subunit, which is analogous to compound A in the Guidelines that inhibits enzyme XYZ. The present specification states that the Kv10 channels are likely involved in modulating cytoplasmic potassium concentration and cellular functions in the relevant tissues. Thus, the ion channels can be used as targets for treating disorders related to abnormal cellular functions in these tissues. In Example 8 of the Guidelines, claim 1 directed to compound A is found to have utility even though there is no disclosure of

specified disease to be treated. Accordingly, even if the Examiner is not convinced that the Kv10 channels are involved in regulation of intracellular potassium levels and cellular function in tissues expressing the channels, a claim directed to compound A, *i.e.*, the nucleic acid encoding a Kv10 channel subunit in the present case, has sufficient utility for patentability. The utility resides in the fact that the polypeptides encoded by the claimed nucleic acids are voltage-gated potassium channels subunits, which, like enzymes, have a well-established utility in the art: modulating the passage of potassium ions according to varying conditions.

In response to the third argument, Applicant contends that, by teaching the use of a Kv10 channel for screening its modulators having therapeutic applications, the specification does provide a "clear understanding of how to use the polypeptide." A person of skill in the art would know, upon reading the present disclosure, how to conduct activity assays for a Kv channel, and therefore know exactly "how to use the polypeptide" in the screening for its modulators. It should be again emphasized that the utility of a polypeptide, which can be used for identifying its modulators, and the utility of the modulators so identified must be distinguished in order to ensure an appropriate utility assessment.

In summary, Applicant does not believe that the utility rejection is proper and therefore respectfully requests its withdrawal.

B. 35 U.S.C. §112, First Paragraph

Utility-Based Enablement Rejection

Claims 12-14 and 16-18 also stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement due to the lack of patentable utility as required by 35 U.S.C. §101. As stated in the section above, the claimed invention fully complies with the utility requirement under 35 U.S.C. §101, Applicant contends that the enablement rejection on this ground is improper and respectfully requests its withdrawal.

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Amdt. dated April 18, 2007
Reply to Final Office Action of August 23, 2006

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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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